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Original Article

Characterization of atrial fibrillation and the effect of pulmonary vein antrum isolation in endurance athletes

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ABSTRACT

Introduction: Endurance sports have recently been recognized as a risk factor for atrial fibrillation (AF). This study aimed to characterize AF in endurance athletes and to examine the efficacy of pulmonary vein antrum isolation (PVAI) in an attempt to clarify the mechanism.

Methods and results: Twenty-two men (46 ± 8 years old) with AF, who had no risk factors other than participation in long-term endurance sports, were examined; 12 patients had paroxysmal AF, 9 had persistent AF, and 1 had long-standing AF. Twelve patients (55%) were asymptomatic at rest. Nineteen patients (86%) experienced less exercise tolerance during AF than during sinus rhythm; exercise-induced paroxysmal AF was noted in 14 of these patients (64%). Antiarrhythmic drugs (AADs) were used in 18 patients, but were effective in only 3 patients (16%). Eleven patients underwent PVAI; in these patients, AF was eliminated without AADs in 9 patients (82%) and with AADs in 2 patients over an average follow-up period of 21 ± 9 months.

Conclusion: AF in endurance athletes is frequently asymptomatic at rest, but manifests as reduced exercise tolerance. AF originates from the pulmonary veins; PVAI could be an effective non-pharmacologic therapy.

1. Introduction

Long-term endurance sports have recently been recognized as one of the risk factors for atrial fibrillation (AF) [1–8]; widely accepted risk factors for AF include age, hypertension, diabetes mellitus, structural heart disease, hyperthyroidism, obesity, and heavy alcohol intake [9–12], although moderate physical activity may decrease the risk of AF [13]. Elosua et al. [4] reported that a lifetime of sport activities of at least 1500 h is associated with a higher risk of AF, and there are increasing data that AF is 2–10 times more prevalent in active or former athletes in Europe and America [1–8]. A substantial number of endurance athletes experience AF in Japan, which may be explained by the rise in popularity of jogging among the Japanese, but the connection remains unclear.

AF has been reported to originate in the pulmonary vein (PV) in the majority of patients with paroxysmal AF and in a substantial number of patients with persistent AF [14,15]; PV antrum isolation (PVAI) eliminates AF in these patients [16,17]. However, the mechanism underlying the relationship of AF with endurance sports remains unclear, and there are limited data regarding the efficacy of PV isolation for AF [18,19]. Therefore, this study aimed to characterize AF in endurance athletes and to examine the efficacy of PVAI in an attempt to clarify the mechanism.

2. Methods

2.1. Patients

This study included 22 male athletes with AF (age, 46 ± 8 years; range, 32–54 years). Athletes were defined according to previously described criteria [4] as individuals who had performed endurance sports for more than 3 h per week for at least 10 years prior to the arrhythmia diagnosis. All patients were dedicated to endurance sports, including daily jogging, swimming, and skiing; 12 patients (55%) had completed full marathons.

In all patients, transthoracic echocardiography and/or cardiac magnetic resonance imaging (MRI) were performed to exclude underlying structural heart diseases, measure cardiac chamber

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size, and evaluate the left ventricular function. Those having other risk factors of AF, such as age (> 65 years), hypertension, diabetes mellitus, structural heart disease, hyperthyroidism, obesity, and heavy alcohol intake [9–12], were excluded from this study. AF was classified as paroxysmal, persistent, or long-standing according to the definitions of the consensus statement on catheter and surgical ablation of AF [20].

For 11 of the 22 patients who underwent PVAI to treat AF, AF-related symptoms reduced their exercise tolerance and limited their activities in sports.

2.2. Pulmonary vein antrum isolation

After giving informed consent, all 11 patients underwent an electrophysiological study in a fasting and conscious sedated state. All antiarrhythmic drugs (AADs) were discontinued for at least 5 half-lives prior to the study. PVAI was performed using a deflectable 7-Fr quadripolar, non-irrigated 8-mm tip electrode ablation catheter (Fantasista™; Japan Lifeline Co. Ltd., Tokyo, Japan) under navigation using EnSite Array™ (N=5) or EnSite NavX™ (N=7) (St. Jude Medical, St. Paul, MN, USA). The details of PVAI performed using EnSite Array™ or NavX™ have been described elsewhere [21–24]. In addition to PVAI, linear ablation at the tricuspid isthmus was performed in all patients.

2.3. Follow-up after PVAI

For follow-up examinations after PVAI, patient visits occurred at the outpatient clinic at 2 weeks, 1 month, and every 1–3 months thereafter. A 12-lead electrocardiogram was recorded at each visit. Routine 24-hour Holter monitoring was performed 3 months after PVAI and every 6 months thereafter; at least 1 treadmill exercise test was performed 6 months after PVAI. During 24-hour Holter monitoring, the patients were asked to perform their usual sports activities to allow detection of atrial tachyarrhythmia recurrence. Any symptomatic or asymptomatic atrial tachyarrhythmia was considered recurrence. When a recurrence was observed and the patient agreed, a second session was performed. AADs were continued for at least 3 months and then tapered off by 6 months.

2.4. Statistical analysis

Continuous variables are expressed as the mean ± SD or number and percentage, as appropriate. Continuous variables were compared using the Student's *t*-test for paired and unpaired comparison, when appropriate. Categorical variables were compared with a Fisher's exact test. Results with a p value of < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The baseline characteristics of the 22 patients are shown in Table 1. None of the patients had structural heart disease. The baseline heart rate during sinus rhythm was 52 ± 9 beats per minute (bpm), and the baseline heart rate during AF at rest was less than 80 bpm in 11 patients (50%) without any rate-control drugs. Twelve patients had paroxysmal AF. Nine patients had persistent AF lasting for > 1 week (range: 1 week to 12 months), and 1 patient had long-standing AF for 7 years. Of these 10 patients, 5 had persistent AF at the time of the diagnosis; in the remaining 5 patients, paroxysmal AF progressed to persistent (N=4) or long-standing AF (N=1) over the course of the study.

Table 1
Characteristics of Study Patients.

Patient number	N=22
Age (years, range)	46 ± 8 (32–54)
Male gender	22 (100%)
Type of AF	
Paroxysmal	12 (55%)
Persistent	9 (41%)
Long-standing	1 (5%)
History of AF (years)	4.2 ± 3.0
LAD (mm)	39 ± 6 (32–49)
LVEDD (mm)	53 ± 4
LVESD (mm)	33 ± 4
LVEF (%)	67 ± 7
BMI (kg/m^2)	23.3 ± 2.3
Sinus rate at rest (bpm)	52 ± 9

AF=atrial fibrillation; BMI=body mass index; bpm=beats per minute; LAD=anteroposterior left atrial diameter; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter.

3.2. Symptoms and medical treatments

All 22 patients had symptoms including palpitation and decreased exercise tolerance (e.g., earlier manifestation of shortness of breath than before, easy fatigability, and chest discomfort during exercise). It was noted that palpitation was less prevalent (N=8, 36%) and, when present, the magnitude was mostly weak and the main manifestations were exercise-related. Twelve patients (55%; 4 paroxysmal, 7 persistent, and 1 long-standing AF) had no symptoms at rest or during mild exertion, whereas 19 (86%) patients developed AF-related symptoms during exercise. It should be emphasized that 14 patients (64%) had exercise-induced AF, which was revealed by a treadmill exercise test (N=5) or was suggested by the sudden onset of symptoms during exercise (N=9), including reduced exercise tolerance, shortness of breath, and chest discomfort. Furthermore, paroxysmal AF occurred at night or after meals in 5 patients; 2 of these patients also had exercise-induced AF.

Fig. 1 shows an example of paroxysmal AF in an endurance athlete. The patient was a 40-year-old marathon runner, and the 12-lead electrocardiography exhibited repetitive paroxysmal AF with short durations. He was not treated previously because he had no symptoms; despite having AF, the patient exhibited a normal range of heart rate with a relatively regular RR interval. However, 2 years later, he felt a sudden impairment of exercise sustainability during running, and he was diagnosed with paroxysmal AF. Fig. 2 shows another example of paroxysmal AF that occurred during a treadmill exercise test in a 53-year-old jogger. Premature atrial contraction repetitively occurred at 3 min and 30 s after the beginning of exercise and AF eventually developed at 7 min and 40 s, which was self-terminated after the exercise.

AADs, such as bepridil (N=9) and pilsicainide (N=15), were prescribed in 18 patients (82%), but effectively suppressed AF in only 3 patients with paroxysmal AF (17%) during an observation period of 4.4 ± 3.2 years. Although AADs were effective in the beginning of the observation period, they tended to become ineffective over time. Amiodarone and sotalol were not prescribed to any patients. AADs were not prescribed to 4 patients (paroxysmal=2, persistent=2) because their symptoms were mild except during exercise. Atrial flutter (AFL) was documented in 5 patients (23%) under no AAD (N=1) or after oral pilsicainide (N=4), which failed to suppress the AFL. Beta-blockers were not well tolerated in most patients because they exacerbated the loss of exercise tolerance.

In one typical case of exercise-induced paroxysmal AF, the patient's heart rate during exercise-induced AF became > 250 bpm, although the sinus rate at rest was < 60 bpm. The patient was prescribed bisoprolol (2.5 mg, once a day) to suppress his exercise-induced AF. A week later, the AF persisted and the heart rate

Fig. 1. Twelve lead electrocardiograms were recorded from a 40-year-old marathon runner. Atrial premature contractions and AF with short duration were recorded (arrows). He had no symptoms during rest and exercise at the time, but 2 years later, he experienced symptomatic exercise-induced paroxysmal AF. AF was completely eliminated by PV antrum isolation.

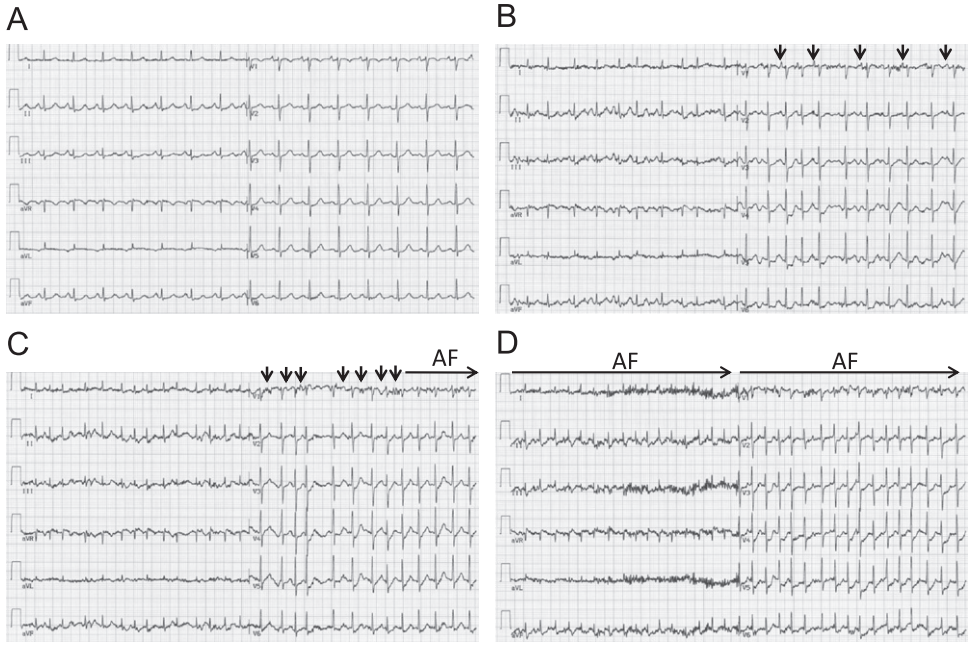

Fig. 2. Exercise-induced atrial fibrillation (AF) during a standard Bruce protocol in a 53-year-old man. Twelve-lead electrocardiograms at 1:30 min (panel A), 3:30 mins (panel B), 7:40 mins (panel C), and 8:00 min (panel D) are shown; the left half of each panel shows limb leads and the right half shows precordial leads. At 3:30 min after the start of exercise, atrial premature contractions were observed (arrows) and AF eventually developed (panel C). At 8:00 min, the patient complained of shortness of breath and chest discomfort, although he had no symptoms before the AF occurrence.

decreased to <60 bpm at rest despite the AF. The patient showed orthostatic hypotension and felt constant fatigue, possibly due to bradycardia. Although transthoracic echocardiography exhibited normal left ventricular function, the blood concentration of brain natriuretic peptide (BNP) increased to 307 pg/ml (normal range, <18 pg/ml). After cessation of bisoprolol, his condition returned to the previous level and the BNP concentration decreased to 49 pg/ml.

3.3. Pulmonary vein antrum isolation

Eleven out of the 22 patients underwent PVAI (PVAI patients), but the remaining 11 patients did not agree to the catheter ablation (non-PVAI patients). All of the PVAI patients complained of less exercise tolerance. AADs were not effective in any of the patients. We compared the clinical characteristics between PVAI patients and non-PVAI patients. There were no significant differences in the clinical characteristics between the 2 groups (Table 2).

Focal activities, which triggered AF, were observed in the pulmonary veins in 8 patients (73%). Fig. 3 shows that the antrum isolation of the left inferior PV under navigation using the EnSite Array resulted in AF termination in the atrium while localized AF persisted only in the left inferior PV, suggesting that the left inferior PV is responsible for maintaining AF. In addition to PVAI, a linear ablation at the tricuspid isthmus was performed in all patients. In 10 patients, no other ablative procedures were performed. In 1 patient with persistent AF lasting for >6 months, additional left atrial (LA) line creations at the LA roof and septum were performed following PVAI because AF was not eliminated by PVAI alone. In all patients, electrical isolation of all 4 PVs was achieved without any complications.

Table 2
Comparisons of PVAI and non-PVAI patient characteristics.

	PVAI patients $N=11$	Non-PVAI patients $N=11$	P value
Age (years)	45 ± 7	47 ± 7	0.5486
Type of AF			
Paroxysmal	5 (45%)	7 (64%)	0.3870
Persistent	6 (55%)	3 (27%)	
Long-standing	0 (0%)	1 (9%)	
Duration of AF persistence (months)[a]	3.3 ± 2.8	6.0 ± 7.1	
History of AF (years)	4.4 ± 2.4	3.8 ± 3.8	0.8316
LAD (mm)	39 ± 4	39 ± 7	0.9705
LVEDD (mm)	53 ± 5	53 ± 4	0.6700
LVESD (mm)	33 ± 5	34 ± 4	0.6702
LVEF (%)	67 ± 9	68 ± 6	0.7898
BMI (kg/m^2)	23.0 ± 2.4	24.0 ± 2.4	0.5474
Sinus rate at rest (bpm)	53 ± 6	53 ± 11	0.8903

PVAI=pulmonary vein antrum isolation; AF=atrial fibrillation; BMI=body mass index; bpm=beats per minute; LAD=anteroposterior left atrial diameter; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter.

[a] Cases are limited in patients with persistent AF.

3.4. Results of PVAI

After the first session, paroxysmal AF recurred in 3 out of 11 patients (27%). One patient, who had persistent AF lasting for >6 months before PVAI, underwent second and third sessions; in every session, some LA–PV reconnections were observed and PVAI was repeated until no AF recurrence was detected. The remaining 2 patients, who had AF recurrence, did not undergo additional sessions because a previously unsuccessful AAD could suppress the AF after the first session, which allowed them to resume their sports activities.

After the final session, 9 patients (82%) had no recurrence of AF and were not prescribed AADs. The exercise tolerance returned to the previous level in all patients during the 21 ± 9 month follow-up. In addition, transthoracic echocardiography revealed that the LA diameter significantly decreased from 39 ± 4 mm to 35 ± 2 mm after the PVAI ($p=0.0224$), although the left ventricular diastolic and systolic diameter and the ejection fraction did not change. The heart rate during sinus rhythm at rest obtained at the outpatient clinic significantly increased from 51 ± 7 bpm before PVAI to 62 ± 9 bpm ($p=0.0016$) at 12 ± 2 months after the PVAI.

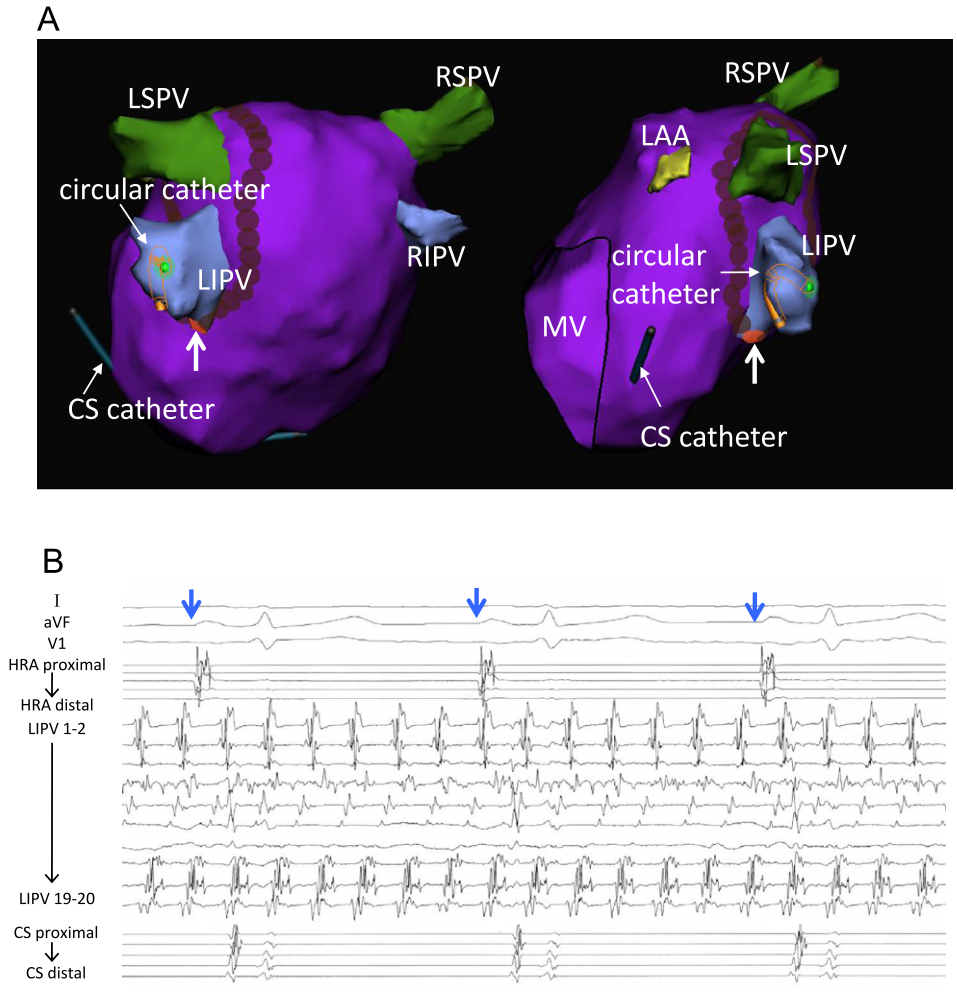

Fig. 3. Pulmonary vein antrum isolation (PVAI) and the termination of AF in a 42-year-old man. The upper panel shows the geometry of the left atrium from the posterior aspect (left) and left aspect (right). The brown tags indicate the ablation lines along the left ipsilateral PV (LIPV) antrum. The orange tags, just below the LIPV (red arrows), indicate the point where the electrical isolation of the PV was performed. The PVAI resulted in the termination of AF in the left and right atrium, but localized AF persisted within the LIPV. Panel B shows the electrocardiograms at leads I, aVF, and V1 and the intracardiac electrograms in the high RA (HRA proximal to distal) and coronary sinus (CS proximal to distal). Blue arrows indicate the sinus rhythm in the right atrium and coronary sinus; electrograms recorded at the circular catheter in the LIPV (LIPV 1–2 to 19–20) exhibited localized AF. AF=atrial fibrillation, CS=coronary sinus, HRA=high right atrium, LA=left atrium, LAA=left atrial appendage, LIPV=left inferior pulmonary vein, LSPV=left superior pulmonary vein, MV=mitral valve, RA=right atrium, RIPV=right inferior pulmonary vein, RSPV=right superior pulmonary vein. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

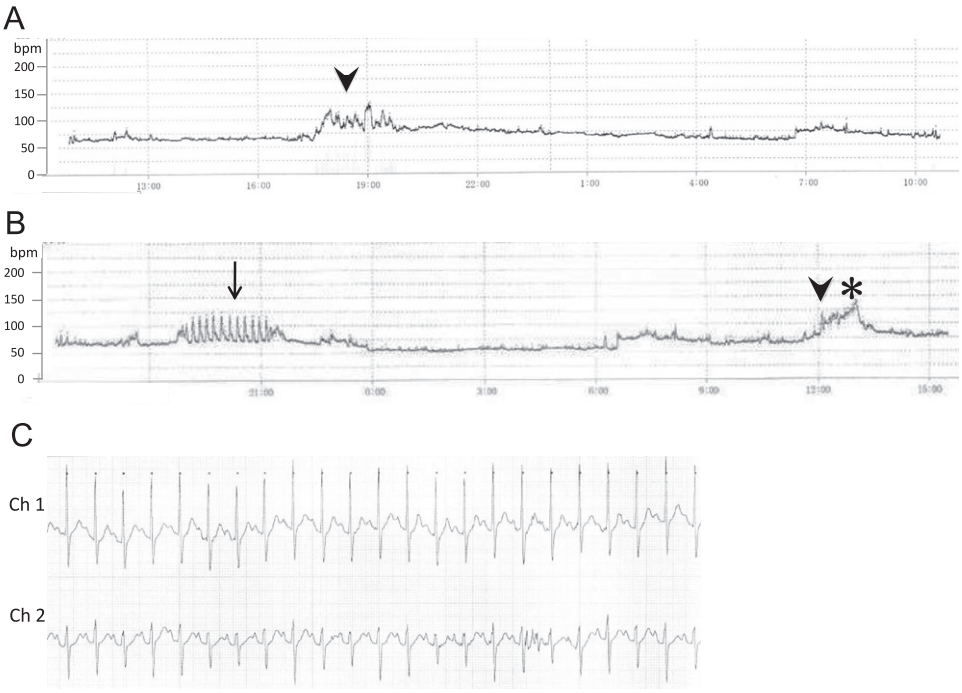

Fig. 4. Holter electrocardiographic recordings after pulmonary vein antrum isolation (PVAI) in a 54-year-old man. The trendgrams of heart rate at 6 months (Panel A) and 12 months (Panel B) after PVAI are shown. The arrowheads in panels A and B indicate that the heart rate increased during jogging. The arrow in panel B indicates repetitive sudden increases in the heart rate, which was due to skiing not AF; the heart rate repeatedly increased when skiing down a slope and it decreased when riding the ski lift up a hill. Panel C shows electrograms at a maximum heart rate of 142 bpm during jogging (the timing of the asterisk in panel B), which shows sinus tachycardia. No atrial tachyarrhythmia was documented by Holter electrocardiographic recordings, even during exercise. bpm = beats per minute.

Fig. 4 shows heart rate trendgrams and electrocardiographic recordings after PVAI in a 42-year-old male patient with persistent AF lasting for >6 months. The heart rate trendgrams obtained by Holter monitoring at 6 months and 12 months after the PVAI exhibited no AF recurrence during exercise. His exercise tolerance returned to the previous level during sinus rhythm.

Regarding the clinical course of non-PVAI patients, 1 paroxysmal AF patient progressed to persistent AF and 1 persistent AF patient progressed to long-standing AF during the follow-up period of 24 months, despite the use of AADs.

4. Discussion

4.1. Main findings

Most endurance athletes with AF experience decreased exercise tolerance during their endurance sports activities although half of them have no symptoms during rest or mild exertion. AADs, including bepridil and sodium channel blockers, are not effective in the majority of patients. Here, we showed that PVAI eliminated AF in most patients, suggesting that the mechanism of AF seems to be linked to focal activities originating from the pulmonary veins.

4.2. Atrial fibrillation in athletes

Published reports have linked autonomic nerve activity to the occurrence of AF. In this study, 14 patients (64%) had exercise-induced AF while 5 patients (23%) had AF episodes at rest or after meals; the former seems to relate to increased sympathetic nerve activity and the latter to increased vagal nerve activity. In endurance athletes, vagal tone seems to be increased at rest [25], which is suggested by both slow heart rates during sinus rhythm and slow ventricular rates during AF. Clinical and experimental data show that increased vagal nerve activity shortens the atrial refractory period inhomogeneously by increasing the I_{k-Ach} current and increases the dispersion of the atrial refractory period, facilitating reentry [26,27]. In contrast, increased sympathetic nerve activity is also reported to shorten the atrial refractory period and increase the dispersion by increasing the I_{ks} current, which facilitates reentry and late phase 3 early after depolarization by increasing the I_{Ca-L} and Ca^{2+} release from the sarcoplasmic reticulum [28].

The maintenance of AF requires not only an initiator but also an AF substrate, including atrial fibrosis, loss of gap junctions, and LA enlargement [29,30]. Long-term endurance sports cause LA enlargement. In fact, athletes have a larger atrium compared to sedentary controls [31,32]. Subsequent increases in the LA wall strain and/or stretch are reported to relate to AF maintenance [25]. In this study, mean LA dimension was 39 ± 6 mm (range, $32-49$ mm), which seems higher than control subjects of similar age and the same sex. Furthermore, it is reported that athletes show higher levels of collagen markers, including plasma PICP, CITP, and TIMP-1, when compared with sedentary controls [33]. Therefore, endurance athletes seem to be prone to AF. The European Society of Cardiology (ESC) guidelines for the management of patients with AF reported that people who perform endurance sports, especially competitive sports, are likely to develop AF [34].

4.3. Pharmacological treatment

The easiest and least expensive therapy for AF in endurance athletes would be to stop exercising [34], which is always very difficult. The ESC guidelines for the management of patients with AF report that competitive athletes are difficult to manage because many of the treatment options are not allowed and the recommendation to reduce exercise is not easily accepted. In our experience, the patients usually refused to cease or reduce their exercise

because sports play an important role in their lives and they are passionate about sports activities.

Although class 1C agents, such as flecainide or propafenone, are recommended in general [25,34], AADs were usually ineffective in the majority of the patients in this study. In many cases, the drugs were effective at the beginning of treatment, but became gradually ineffective with time. Furthermore, oral administration of sodium channel blockers led to AFL in some patients, which aggravated their symptoms and worsened their quality of life. In extreme situations, the atrial rate of AFL is decreased by AADs; thus, one-to-one atrioventricular conduction may occur during exercise. In contrast, the use of beta-blockers to control rate during AF is usually not acceptable because the exercise intolerance is exacerbated due to inappropriate heart rate response and negative inotropic effects. Further, beta-blockers worsen their bradycardia at rest, which sometimes causes dizziness and general fatigue or even heart failure due to the combination of negative inotropic effects and extreme bradycardia.

4.4. Catheter ablation for AF

We performed PVAI in 11 patients with drug refractory AF. No recurrence was noted after PVAI without AAD in 9 patients, but 1 patient required 3 sessions to eliminate AF. In the other 2 patients, an AAD suppressed AF after a single PVAI. All patients felt that their exercise tolerance returned to previous levels after the PVAI. Therefore, PVAI should be a preferable treatment option, especially for athletes with paroxysmal AF or early-stage persistent AF, as long as the patients have significant symptoms and wish to continue their sports activities without impairment of exercise tolerance.

However, for athletes with AF, there are important differences to consider prior to performing PVAI. First, the atrial wall of endurance athletes may be thicker than that of sedentary patients. We have observed that it is sometimes challenging to make a transmural lesion by radiofrequency energy delivery at the PV antrum in endurance athletes compared with sedentary patients. Second, recurrences are often observed after a single session [18,19] and repeated procedures would be required. Third, they receive catheter ablations to resume endurance sports at full intensity. Attention should be paid to avoid complications such as PV stenosis and phrenic nerve injury, because these complications may lead to impairment of exercise tolerance even if their magnitude is mild.

4.5. Limitations

The main limitation of this study is the small size of the study population. Therefore, the indications for PVAI should be considered carefully. However, PVAI should be effective to control AF in endurance athletes. In addition, we evaluated the exercise tolerance only on the basis of subjective symptoms. However, objective evaluations, such as cardiopulmonary exercise testing, could be performed to accurately evaluate the exercise tolerance.

5. Conclusion

AF is asymptomatic at rest in about half of the patients, but it manifests as less exercise tolerance in the majority of patients. It is frequently induced by exercise and usually drug refractory. AF originates from the PVs and PVAI could be an effective therapy for AF in athletic patients as well as non-athletic patients.

Conflict of interest

Dr. Tsuchiya has served as a speaker and consultant for Nihon Kohden and St. Jude Medical.

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